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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/320,609	05/26/99	WILUSZ J	601-1-088N

HM12/0426

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EXAMINER	
SIU,S	
ART UNIT	**PAPER NUMBER**
1631	9

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/320,609	WILUSZ ET AL.	
	Examiner	Art Unit	
	Stephen C Siu	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Specification

The Brief Description of the Drawings have been amended to correct improper reference to panels in the figures. Therefore, the objection to the Brief Description of the Drawings for improper reference to the figures has been withdrawn.

Sequence Rules

Acknowledgement of the paper and disk copy of the sequences is made, as well as the statement that the contents are the same. Therefore, objection to non-compliance to the requirements of 37 C.F.R. 1.821-1.825 is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 21-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended the claims to recite a method for identifying an agent capable of modulating the *in-vivo* stability of a target RNA sequence, however, there is no support in the specification for screening of agents that modulate *in-vivo* stability of target RNA sequence. The specification only provides support to in-vitro modulation of RNA turnover.

The rejections of claims 2, 7, 9, 10, 12, 15, 21, 26, 27, 48, 51 and 55 under 35 U.S.C. 112, second paragraph in the Office Action mailed November 8, 1999 are withdrawn in view of the amendment received February 11, 2000.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 recites "said labeled target RNA" which lacks antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 3 has been canceled; therefore, the rejection of claim 3 under 35 U.S.C. 102(b) has been withdrawn.

Claims 1-2, 8-10, 12-15, 21, 24-30, and 51-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Bernstein (Molecular and Cellular Biology, Feb. 1989, Vol.9, No.2, pages 659-670) for reasons of record in the Office Action mailed November 8, 1999.

Applicant's arguments filed February 22, 2000 have been fully considered but they are not persuasive. As the Applicant states, Bernstein teaches the use of a component of a cell extract obtained from eukaryotic cells in an mRNA decay system. The term "cell extract" recited in the claims is interpreted broadly as a component of the cell following, for example, lysis of the cell. Bernstein utilized "cell extracts" (see abstract, line 2) in an in vitro mRNA decay system. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which the applicant relies (i.e., cell extract does not comprise an isolated cell fraction and nuclei and nuclear contents and ribosomes excluded by centrifugation at 100,000 x g) are not recited in the rejected claims(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed.

Cir. 1993). Therefore, Bernstein reads on the claimed invention. Also, Applicant has amended the claim to recite "[t]urnover comprises deadenylation and degradation" and states that Bernstein does not teach deadenylation of RNA. However, Bernstein states on page 661, col.2, paragraph 2 that in observations, "mRNA decay intermediates were observed in reactions...one..class corresponded to mRNA molecules whose poly(A) tracts were being shortened...[t]he second...migrated...at the same position as deadenylated mRNA...These intermediates suggest a stepwise decay pathway in which the poly(A) is first shortened and then removed and...the deadenylated mRNA is then completely destroyed". Therefore, Bernstein demonstrates deadenylation and the rejection under 35 U.S.C. 102(b) is maintained.

Claims 1, 4-6, 12, 14, 16-17, 21-25, 28 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Krikorian (Journal of Virology, Jan. 1991, Vol.65, pages 112-122) for reasons of record in the Office Action mailed November 8, 1999.

Applicant's arguments filed February 22, 2000 have been fully considered but they are not persuasive. Applicant states that the Krikorian system did not utilize any source of exogenous RNA in contrast to the instantly claimed invention in which the RNA studied is from an exogenous source. However, Krikorian demonstrates the decay of exogenous GAPD mRNA and total 28S rRNA (see Fig. 7 and page 117, col.2, lines 11-12). Applicant states that Krikorian does not demonstrate deadenylation of mRNA. However, deadenylation is an inherent property of mRNA degradation as evidenced by

the teachings of, for example, Bernstein (see above) wherein deadenylation precedes degradation of mRNA. Krikorian examines degradation/decay of mRNA and therefore, necessarily performs deadenylation of the RNA. Finally, Applicant maintains that the Krikorian observations on RNA turnover were made on only infected cells as the source of extract and not uninfected cells and therefore differs from the claimed invention. However, the claims are drawn to cells that are either infected or uninfected. Therefore, the claim(s) read on the teachings of Krikorian. The rejection under 35 U.S.C. 102(b) is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein (Molecular and Cellular Biology, Feb. 1989, Vol.9, No.2, pages 659-670) in view of Brewer (Mol and Cell Biol., Vol.3, No.4, Apr 1988, pages 1697-1708) and in further view of Krikorian (J of Virology, Jan.1991, Vol.65, pages 112-122).

Bernstein demonstrates a system and method for evaluating the effect of exogenously added agents (PABP) on the stability of poly(A) mRNAs. A system comprising target RNA and cell extract depleted of poly(A) binding protein is utilized

wherein exogenous PABP is introduced into the system and the effect of PABP on the resulting degradation of mRNA is evaluated. Bernstein states on page 661, col.2, paragraph 2 that in observations, "mRNA decay intermediates were observed in reactions...one..class corresponded to mRNA molecules whose poly(A) tracts were being shortened...[t]he second...migrated...at the same position as deadenylated mRNA...These intermediates suggest a stepwise decay pathway in which the poly(A) is first shortened and then removed and...the deadenylated mRNA is then completely destroyed". Bernstein further states that "inhibitors that interfere with polyadenylation can affect other ATP-dependent processes..." thus indicating that ATP-dependent processes are performed in the process of mRNA degradation.

Bernstein does not explicitly teach monitoring of deadenylation of target RNA.

Brewer demonstrates a system and method for monitoring deadenylation and degradation of target RNA and teaches that poly(A) shortening precedes degradation of mRNA with AU-rich sequences at the 3' end.

Brewer does not specifically teach the addition of nucleotide triphosphate to the system of mRNA turnover.

Krikorian demonstrates the use of an in vitro mRNA degradation system, the system comprising target mRNA and cell extract, In an experiment to determine whether virion host shutoff-induced in vitro mRNA degradation was dependent upon the components of an energy-generating system, parallel in vitro degradation experiments were conducted in which half of the reactions contained all of the components of the

standard reaction, including ATP, GTP, etc, and the other half did not contain these elements. The degradation of mRNA was then observed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a system of evaluating mRNA decay in the presence of a nucleotide triphosphate, then introduce an agent to evaluate the ensuing effects on the adenylation of target RNA because the system of Bernstein was demonstrated as being successful in evaluating exogeneously introduced agents introduced into the system and observing the resulting effect on mRNA stability by monitoring the degradation of the mRNA. Bernstein further teaches that degradation of mRNA is preceded by deadenylation and that polyadenylation is an ATP-dependent process and indicates the presence of other ATP-depended processes present in the procedure. Brewer further teaches a system that monitors deadenylation of mRNA and that poly(A) shortening precedes degradation of mRNA with AU-rich sequences. Krikorian demonstrates the use of ATP, GTP, etc. in the performance of evaluation of mRNA turnover in his system. One of ordinary skill in the art would have been motivated to utilize the system of Bernstein for evaluating mRNA deadenylation (and degradation) with a nucleotide triphosphate as an energy source of required energy for ATP-dependent steps in the process with a reasonable expectation of success in light of the combined teachings of Bernstein, Brewer and Krikorian that deadenylation precedes degradation in mRNA degradation and that ATP-dependent steps are present in the process and in light of the

successful demonstration of Krikorian of the use of ATP in an in vitro system to evaluate mRNA turnover.

Claims 31-32 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein (Molecular and Cellular Biology, Feb. 1989, Vol.9, No.2, pages 659-670) in view of Chen (Mol.Cell.Biol. Oct 1995, 15(10), pg 5777-88) and in further view of any one of Zhang (Mol.Cell.Biol, Dec 1998, Vol.13, No.12, pages 7652-65), Myer (EMBO, Vol.16, No.8, 4/15/97, pages 2130-2129), Nakagawa (Proc Natl Acad Sci USA, Vol.12, march 1995, pp 2051-55), Levine (Mol. Cell Biol., Vol.13, No. 6, June 1993, pages 3494-3504), Nagy (J of Bio Chem, Vol, 270, No. 6, 2/10/95, pages 2755-2763), Nakamaki (J of Cell Physio., Vol.165, No.3, Dec 1995, pages 484-492), or Liu (Neurology, Vol.45, 3/95, pages 544-550) for reasons of record in the Office Action mailed November 8, 1999.

Applicant's arguments filed February 22, 2000 have been fully considered but they are not persuasive. Applicant further states that the Bernstein reference never examined RNA deadenylation and therefore is not applicable to the present invention. However, Bernstein states on page 661, col.2 that "mRNA decay intermediates were observed in reactions...one..class corresponded to mRNA molecules whose poly(A) tracts were being shortened...[t]he second...migrated...at the same position as deadenylated mRNA...These intermediates suggest a stepwise decay pathway in which the poly(A) is first shortened and then removed and...the deadenylated mRNA is then

completely destroyed". Therefore, Bernstein demonstrates deadenylation and the rejection under 35 U.S.C. 103(a) is maintained.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein (Molecular and Cellular Biology, Feb. 1989, Vol.9, No.2, pages 659-670) in view of Brewer (Mol and Cell Biol., Vol.3, No.4, Apr 1988, pages 1697-1708) and in further view of Krikorian (J of Virology, Jan.1991, Vol.65, pages 112-122) for reasons of record in the Office Action mailed November 8, 1999.

Applicant's arguments filed February 22, 2000 have been fully considered but they are not persuasive. Applicants submit that no previous reference demonstrated RNA turnover (deadenylation and degradation). However, Bernstein teaches RNA turnover (deadenylation and degradation) as stated above. Therefore, the combination of teachings of Bernstein, Brewer and Krikorian would render the claimed invention obvious as described. In light of the above, the rejection of claim 47 under 35 U.S.C. 103(a) is maintained.

Claims 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein (Molecular and Cellular Biology, Feb. 1989, Vol.9, No.2, pages 659-670) in view of Krikorian (J of Virology, Jan. 1991, Vol.65, pages 112-122) for reasons of record in the Office Action mailed November 8, 1999.

Applicant's arguments filed February 22, 2000 have been fully considered but they are not persuasive. Applicant has amended the claims to recite a kit for monitoring the stability of a preselected exogenous target RNA sequence , said kit comprising a cell extract supernatant. Bernstein performs RNA deadenylation and degradation with a cell extract isolated from eukaryotic cells or tissues resuspended in a salt wash that is depleted of activity of proteins that bind polyadenylate but does not demonstrate the procedure utilizing a supernatant. Bernstein provides one of ordinary skill in the art the motivation to monitor RNA turnover utilizing a cell extract depleted of activity of proteins that bind polyadenylate. Krikorian performs RNA degradation utilizing a cell extract supernatant isolated from eukaryotic cells. Krikorian demonstrates the method of monitoring stability of RNA utilizing a cell extract supernatant thus provides the motivation to one of ordinary skill in the art to utilize a cell extract supernatant in monitoring RNA turnover. Through the combined teachings of Bernstein and Krikorian, it would have been obvious to one of ordinary skill in the art to assemble the necessary ingredients of a cell extract supernatant depleted of the activity of proteins that bind polyadenylate and other reagents into a kit to facilitate the procedure with a reasonable expectation of success. Further, the addition of the term "exogenous" to "target RNA sequence" reads on the intended use of the kit and is not given patentable weight. Therefore, the rejection of claims 53 and 54 under 35 U.S.C. 103(a), amendments notwithstanding, is maintained.

The amendment to claims 21 and 33 to add the term "in-vivo" to "stability" is considered new matter (see above) but the amendment is not considered to affect the steps of the claimed invention and the rejection of claims 21, 33 and dependent claims is maintained.

Conclusion

No claims allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stephen Siu, whose telephone number is (703) 308-7522. The Examiner can normally be reached from 7:00 a.m. to 3:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028. Papers related to this application may be submitted to Art Unit 1631 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 308-0294. Please call the Examiner at (703) 308-7522 before the transmission to expedite delivery of the fax. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stephen Siu

04/25/00

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER